# PA: ..NT COOPERATION TREAT.

From the INTERNATIONAL BUREAU

PCT	To:			
NOTIFICATION OF ELECTION (PCT Rule 61.2)	Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2'5C24 Ariington, VA 22202 ETATS-UNIS D'AMERIOUE			
Date of mailing (day/month/year) 01 February 2001 (01.02.01)	in its capacity as elected Office			
International application No. PCT/IB99/01166	Applicant's or agent's file reference 02559PC			
International filing date (day/month/year) 22 June 1999 (22.06.99)	Priority date (day/month/year)			
Applicant				
HAFEN, Ernst				
1. The designated Office is hereby notified of its election made:    X   In the demand filed with the International Preliminary Examining Authority on:   08   January 2001 (08.01.01)				
The International Bureau of WIPO 34, chemin des Colombettes 1211 Genera 20, Switzerland	Authorized officer Olivia TEFY Telephone No.: (41-22) 338-83-38			

by famend post From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY To' E. BLUM & CO. 1 1. DEZ. 2001 NOTIFICATION OF TRANSMITTAL OF Vorderberg 11 THE INTERNATIONAL PRELIMINARY 8044 Zürich EXAMINATION REPORT SUISSE (PCT Bule 71.1) Date of mailing 11.12.2001 (day/month/year) 5011 Applicant's or agent's file reference IMPORTANT NOTIFICATION 02559PC Priority date (day/month/year) International filing date (day/month/year) International application No. 22/06/1999 22/06/1999 PCT/IB99/01166 Applicant

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- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the international Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

## 4. REMINDER

12/12 '01 10:51 FAX +41 1 2516717 PA 7 2001 9:34 EPA MUENCHEN

UNIVERSITĂT ZÜRICH et al.

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The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

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For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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Authorized officer

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# PATENT COOPERATION TREAT

# **PCT**

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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2559PC				***	Priority date (day/month/year)
nternational application No.		on No.	International filing date (day/mor	nuvyear)	22/06/1999
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			eination report has been prepa	red by this In	ternational Preliminary Examining Authority
1. This inte	emati	onal preliminary exam	according to Article 36.		
and is tr	ansm	Illied to are appression			
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2 This RE	POR	T consists of a total of	of 6 sheets, including this cover		
			ied by ANNEXES, i.e. sheets	of the descript	ion, claims and/or drawings which have reotifications made before this Authority
⊠ Thi	s rep	on is also accompan	asis for this report and/or shee	ts containing	rectifications made before this Authority the PCT).
ber	en an Se Ru	le 70.16 and Section	asis for this report and/or shee 607 of the Administrative Inst	uctions under	ne roi).
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1			eleting to the following items:		
3. This re	port	contains indications i	elating to the following items:		
1	521	Basis of the report			
1					
111	-	Non-establishment	of opinion with regard to novel	ty, inventive s	tep and industrial applicability
in iv					
l v	□		a under Article 35(2) with rega	rd to novelty,	inventive step or industrial applicability;
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l vi		Cartain documents	cited		
VII		Certain defects in the	ne international application		
VIII	×	Certain observation	s on the international applicat	ion	
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Date of submission of the demand	Date of completion of this report	
08/01/2001	11.12.2001	
Name and mailing address of the international preliminary examining authority:	Authorized officer	The same of the sa
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d	Lanzrein, M	9)
Fax +49 89 2399 - 4465	Telephone No. +49 69 2399 7358	

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

1.

International application No. PCT/IB99/01166

A	f the report
the red	pard to the elements of the international application (replacement above in this report as "originally filed" aiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)): not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):
	otion, pages: as originally filed
1-44	20 = 1.9 - 1.9
Claim	i, No.:
1-31	as received on 30/08/2001 with letter of 29/08/2001
Draw	ngs, sheets:
1/8-8	as originally filed
Sea	ence listing part of the description, pages:
	as originally filed
The	regard to the language, all the elements marked above were available or furnished to this Authority in the tage in which the international application was filed, unless otherwise indicated under this item.  elements were available or furnished to this Authority in the following language: , which is:  the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)),  the language of publication of the international application (under Rule 48.3(b)),  the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).  Tregard to any nucleotide and/or amino acid sequence disclosed in the international application, the  mational preliminary examination was carried out on the basis of the sequence listing:
×	contained in the international application in written form.
⊠	contained if the international application in computer readable form.
	turnished subsequently to this Authority in written form.
<u>-</u>	turnished subsequently to this Authority in computer readable form.  The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the statement that the subsequently be been furnished.
_	The statement that the subsequency is a statement that the statement that the statement that the information recorded in computer readable form is identical to the written sequence. The statement that the information recorded in computer readable form is identical to the written sequence.
	listing has been fumished.
4. T	e amendments have resulted in the cancellation of:

Form PCT/IPEA/409 (Boxes I-VIII, Sheet 1) (July 1998)

# INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No. PCT/iB99/01166

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EXAMINATION .							
C	_	description, .	ges:				
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ū	] the		eets:				
5. [	<ol> <li>This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):         (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this     </li> </ol>						
	rep	oort.)					
		nal observations, if r			·		
٧.	Reaso citatio	ned statement und ns and explanation	er Article Is suppor	35(2) will ting suct	th regard to novelty, inventive step or industrial applicability; h statement		
1.	Staten	nent					
	Novel	ty (N)	Yes: No:	Claims Claims	<b>1-14, 28-3</b> 1 15-27		
	Inven	tive step (IS)	Yes: No:		1-14, 28-31 15-27		
	Indus	trial applicability (IA)	Yes: No:	Claims Claims	1-31		

2. Citations and explanations see separate sheet

VIII. Certain observations on the International application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

Form PCT/IPEA/409 (Boxes I-VIII, Sheet 2) (July 1998)

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International application No. PCT/IB99/01166 INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET** 

Reference is made to the following documents:

- D1: Leevers, S, et al.: 'The Drosophila phosphoinositide 3-kinase Dp110 promotes cell growth.' EMBO JOURNAL, vol. 15, no. 23, 2 December 1996 (1996-12-02), pages 6584-6594, XP000877417 EYNSHAM, OXFORD GB
- D2: Berg C A; Spradling A C: Studies on the rate and site-specificity of p element transposition. GENETICS 127, 3, 515-524 (1991), cited in the application
- D3: Riesgo-Escovar J. R. et al.: chico, a Drosophila homologue of mammalian insulin receptor substrate (IRS) genes, is required cell-autonomously for cell size. 39th Annual Drosophila Research Conference, 1998: 32, p. a12.

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- The present application relates to Drosophila mutants with reduced body or cell size. Mutations or null alleles of chico result in reduced body size. The chico gene product is a homologue of mammallan insulin receptor substrate (IRS) proteins. Mutant flies are thus useful in screening for compounds interacting with the insulin signalling pathway.
- Novelty (Art. 33 (2) PCT). 2.
- 2.1 Claims 1-14, 28-31 appear to be novel over the cited prior art. Document D1 shows that ectopic expression of a dominant negative mutant of Dp110 (DP110<sup>D964A</sup>) reduced cell size in the wings (Fig. 3) and eyes (Fig. 4) resulting in smaller wings and eyes. Since the claims are restricted to chico mutants, D1 does not affect novelty.

Form PCT/Soparate Sheet/409 (Sheet 1) (EPO-April 1997)

## International application No. PCT/IB99/01166 INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

2.2 Claims 15-27 lack novelty over D2. As revealed in the description p. 3-4, chico1 is a synonym for the P element induced mutation fs(2)41 disclosed in D2. The description states that "two further phenotypes associated with the defect fs(2)41 could be observed: Homozygous animals are reduced in size and adult flies have increased lipid levels". This statement unambiguously reveals that the genotypes of fs(2)41 and chico are the same. Accordingly, it appears that so far undiscovered (or never reported) phenotypic traits of fs(2)41 were found.

For assessment of novelty of the product claims, said phenotypic traits are of no relevance. Said traits represent non-distinctive characteristics which do not imply a particular form of the product. Since the known and claimed products are identical in all respects, an objection of novelty arises (of PCT Guidelines Section IV: III-4.8 and

The same applies with regards to the sequence data included in claims 6,7.

As a consequence of the above, D2 is prejudicial to novelty of the product claims 15-27.

## Inventive step (Art. 33(3) PCT). 3.

Claims 1-14, 28-31 are considered to involve an inventive step within the meaning or Art. 33 (3) PCT.

Said claims concern screening methods using chico mutants.

The meeting abstract D3 describes the phenotype of chico mutants and reveals the function of the gene product as insulin receptor substrate. However, D3 does neither provide any information regarding the gene locus of chico nor does it make a link between fs(2)41 and chico. The information provided in D3 is therefore insufficient for the skilled person to generate chico mutants for use in the screening methods of said

Thus, D3 is not an enabling disclosure and is therefore not considered relevant for evaluation of inventive step of claims.

Starting from D2, the skilled person would not have derived the phenotype of the reduced body size and therefore would not have considered the use of the mutant for the screening methods recited in claims 1-14, 28-31.

Form PCT/Separate Sheet/409 (Sheet 2) (EPO-April 1997)

# International application No. PCT/IB99/01166 INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

# Re Item VIII

Certain observations on the international application

- Claims 15-27 are unclear because the subject-matter for which protection is sought In the present draft, claim 15 refers to an "insect mutant having at most one wild type chico gene". This can be understood as extending to insects having no chico gene at all, i.e. insects which naturally do not have the chico gene and have some mutation in another gene. Thus, claim 15 and appending claims 16-27 cover a large group of insect mutants, for which there is no support (Art. 6 PCT) and which is not unambiguously distinguishable from the prior art (Art. 6 and Art. 33 (2) PCT).
- Claims 1, 2, 4, 5, 12-24, 26-31 are not supported by the description as required by Art. 6 PCT. Said claims refer to mutants of any insect, whereas the examples in the 2. description concern Drosophila mutants only. The contribution of the present application clearly belongs to the field of Drosophila mutants and does not warrant broadening of the whole concept to all insects.
- Claims 1-5, 8, 10-18, 21-31 refer to a chico mutant. The mutant drosophila or insect is specified solely by a name which, however, is meaningless to the person skilled 3. in the art. Although the mutation has been described in the prior art, it has been given other names therein. It is therefore not clear what the subject matter is and the claims are not enabled (Art. 5/6 PCT).

The PCT Guidelines state in Section IV, II-4.16: "The use of proper names or similar words to refer to materials or articles is undesirable insofar as such words merely denote crigin or where they relate to a range of different products. If such a word is used, then in order to satisfy the requirements of Article 5, the product must normally be sufficiently identified without reliance upon the word, to enable the invention to be carried out by a person skilled in the art. However, where such words have become internationally accepted as standard descriptive terms and have acquired a precise meaning (for example "Bowden" cable, "Beliville" washer), they may be allowed without further identification of the product to which they relate.".

Form PCT/Separate Sheet/409 (Sheet 3) (EPO-April 1997)

## Claims

- 1. A method for searching for compounds or mutations interacting directly or indirectly with the insulin signaling pathway, characterized in that a viable chico mutant insect is treated with at least one compound or with at least one mutation generating means, and that the effect of such treatment on the body size and/or cell size and/or development time and/or lipid level is determined whereby alterations of the body size and/or cell size and/or development time and/or lipid level are detectable in at least part of the animal.
- 2. The method of claim 1 characterized in that the viable chico mutant insect comprises at most one 15 wild-type chico gene.
  - 3. The method of claim 2 wherein the mutant is a Drosophila mutant and wherein said mutant is treated in the egg or larvae stadium with said compound or compound generating means.
- 20 4. The method of claim 2 or 3 wherein the mutant does not comprise a wild-type chico gene.
  - 5. The method of claim 2 or 3 wherein the Drosophila mutant comprises one wild-type chico gene.

    6. The method of claim 5 wherein the wild-
- 25 type chico gene encodes the amino acid sequence of Table 1 (SEQ. ID. NO. 2, 3).
- 7. The method of claim 6, wherein the wildtype chico gene is the genomic or the cDNA sequence represented in Table 1 (SEQ. ID. NO. 1, 2) or Table 2 30 (SEQ. ID. NO. 4).
  - 8. The method of anyone of claims 2 to 7 wherein the Drosophila mutant comprises at least one chico mutation with lacking or reduced activity compared to wild-type chico.
  - 9. The method of claim 7 wherein the chico mutation is the mutation described in Figure 3A.



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- 10. The method of anyone of claims 2 to 9 wherein the Drosophila lacks at least one chico gene.
- 11. The method of claim 10 wherein the mutant
- lacks both chico genes. 12. The method of anyone of claims 1 to 11
- wherein the compound is a compound for the treatment of 5 diabetes type 2.
- 13. The method of anyone of claims 1 to 12, wherein the alteration of the body size and/or the cell 10 size and/or the development time and/or the lipid level is detectable in the whole animal.
- 14. The method of anyone of claims 1 to 12, wherein the alteration of the body size and/or the cell size and/or the development time and/or the lipid level 15 is detectable in the head region only.
  - 15. A viable insect mutant comprising at most one wild-type chico gene in at least a part of its body and said at least one part of the body shows reduced size.
- 16. The mutant of claim 15 that does not 20 comprise as sole chico genes two chico genes.
  - 17. The mutant of claim 15 or 16 that does not comprise a wild-type chico gene.
    - 18. The mutant of claim 15 or 16 that
- 25 comprises one wild-type chico gene.
  - 19. The mutant of claim 18 wherein the wildtype chico gene encodes the amino acid sequence of Table 1 (SEQ. ID. NO. 2, 3).
- 20. The mutant of claim 19, wherein the wild-30 type chico gene is the genomic or the cDNA sequence represented in Table 2 (SEQ. ID. NO. 4) or Table 1 (SEQ.
  - ID. NO. 1, 2). 21. The mutant of anyone of claims 15 to 20
- comprising at least one chico mutation with lacking or 35 reduced activity compared to wild-type chico.
  - 22. The mutant of claim 21 wherein the chico mutation is the mutation described in Figure 3A.



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23. The mutant of anyone of claims 15 to 22 lacking at least one chico gene.

24. The mutant of claim 15 lacking both chico

genes.

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25. The mutant of anyone of claims 15 to 24 which is a fly mutant, in particular a Drosophila mutant.

26. The mutant of anyone of claims 15 to 25.

wherein at most one wild-type chico gene is found in the whole body of the insect.

27. The mutant of anyone of claims 15 to 25, 10 wherein at most one wild-type chico gene is found in the

head region of the insect only. 28. Use of an insect according to anyone of claims 15 to 27 as a means in screening compounds for

15 modulating diseases.

29. Use of an insect according to anyone of claims 15 to 27 as a means for searching for mutations involved directly or indirectly in the insulin signaling pathway.

30. Use according to claim 22 or 23,

characterized in that the disease is diabetes type 2. 31. A method for generating a mutant insect,

characterized in that adult animals, in particular males, are treated with a mutation generating means under

25 mutation generating conditions, that thus treated insects are crossed to wild-type or mutant insects, in particular chico mutant insects, and that viable offsprings with altered cell number and /or cell size and/or developmental time and/or lipid levels are cultivated

30 under suitable conditions.



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# PATENT COOPERATION TREATY

From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY by fax and post

## PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

E. BLUM & CO. Vorderberg 11 8044 Zürich SUISSE 1 C. GKT. 2001 N / ...

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Date of mailing (day/month/year)

05.10.2001

Applicant's or agent's file reference

International application No.

PCT/IB99/01166

International filing date (day/month/year) 22/06/1999

IMPORTANT NOTIFICATION

Priority date (day/month/year) 22/06/1999

Applicant

UNIVERSITÄT ZÜRICH et al.

- The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the
  international preliminary examination report and its annexes, if any, established on the international application.
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# **PCT**

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

See Notification of Transmittal of International

Applicant's or agent's file reference		it's file reference	FOR FURTHER ACTI	See Notif ON Prelimina	ication of Transmittal of International ry Examination Report (Form PCT/IPEA/416)				
02559PC									
International application No.		ation No.	International filing date (day/month/year)		Priority date (day/month/year)				
PCT/IB99/	0116	66	22/06/1999		22/06/1999				
International Patent Classification (IPC) or national classification and IPC									
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Applicant	<b>-</b> i -	ZÜRICH et al.							
					LD Universe Examining Authority				
1. This in	erna	tional preliminary exam	ination report has been pre	epared by this In	nternational Preliminary Examining Authority				
and is	trans	mitted to the applicant a	according to Article 36.						
2. This R	EPO	RT consists of a total of	6 sheets, including this co	over sheet.					
			d by ANNEYES in cheet	s of the descript	tion, claims and/or drawings which have rectifications made before this Authority				
(se	en a	le 70.16 and Section 6	07 of the Administrative In	structions under	the PCT).				
These	anne	exes consist of a total of	3 Silects.						
		inc indications rela	ating to the following items	:					
3. This re	роп	contains indications rea	ating to the real						
1	I ⊠ Basis of the report								
- 11		Priority			and industrial applicability				
111				elty, inventive su	ep and industrial applicability				
IV		Lack of unity of inventi	on	and to povolty it	nventive step or industrial applicability;				
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VII			international application						
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Tel. +49 89 2399 - 0 Tx: 523656 epmu d			56 epmu d	Telephone No. +4	9 89 2399 7358				
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Applicant's or agent's file reference

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB99/01166

ı.	Bas	is of the report					
1	<ol> <li>With regard to the elements of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).</li> <li>Description, pages:</li> </ol>						
	1-4	4	as originally filed				
	Cla	ims, No.:					
	1-3	1	as originally filed				
	Dra	wings, sheets:					
	1/8	-8/8	as originally filed				
	Sec	quence listing par	t of the description, pages:				
1-16, as originally filed							
			and the state of t				
	2. Wit lan	th regard to the lan guage in which the	guage, all the elements marked above were available or furnished to this Authority in the international application was filed, unless otherwise indicated under this item.				
These elements were available or furnished to this Authority in the following language: , which is:							
		the language of a	translation furnished for the purposes of the international search (under Rule 23.1(b)).				
		the language of t	publication of the international application (under Rule 48.3(b)).				
		the language of a 55.2 and/or 55.3)	a translation furnished for the purposes of international preliminary examination (under Rule				
	3. Wi	th regard to any <b>nu</b> ernational prelimina	icleotide and/or amino acid sequence disclosed in the international application, the ary examination was carried out on the basis of the sequence listing:				
	⊠	contained in the	international application in written form.				
	⊠	filed together with	h the international application in computer readable form.				
			quently to this Authority in written form.				
		furnished subsec	quently to this Authority in computer readable form.				
		The statement the	nat the subsequently furnished written sequence listing does not go beyond the disclosure i application as filed has been furnished.				
		The statement the listing has been	nat the information recorded in computer readable form is identical to the written sequence furnished.				
	4. Th	ne amendments ha	ve resulted in the cancellation of:				

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB99/01166

		the description,	pages:			
		the claims,	Nos.:			
		the drawings,	sheets:			
5.	This report has been established as if (some of) the amendments had not been made, since they have considered to go beyond the disclosure as filed (Rule 70.2(c)):					
	(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to report.)					

- 6. Additional observations, if necessary:
- V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- 1. Statement

Novelty (N) Yes: Claims 1-14, 28-31 No: Claims 15-27

Inventive step (IS) Yes: Claims 1-14, 28-31

No: Claims 15-27

Yes: Claims 1-31 No: Claims

Citations and explanations
 see separate sheet

Industrial applicability (IA)

# VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

Reference is made to the following documents:

- D1: Leevers, S. et al.: 'The Drosophila phosphoinositide 3-kinase Dp110 promotes cell growth.' EMBO JOURNAL, vol. 15, no. 23, 2 December 1996 (1996-12-02), pages 6584-6594, XP000877417 EYNSHAM, OXFORD GB
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- D3: Riesgo-Escovar J. R. et al.: chico, a Drosophila homologue of mammalian insulin receptor substrate (IRS) genes, is required cell-autonomously for cell size.

  39th Annual Drosophila Research Conference, 1998: 32, p. a12.

## Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- The present application relates to Drosophila mutants with reduced body or cell size.
   Mutations or null alleles of chico result in reduced body size. The chico gene product
   is a homologue of mammalian insulin receptor substrate (IRS) proteins. Mutant flies
   are thus useful in screening for compounds interacting with the insulin signalling
   pathway.
- Novelty (Art. 33 (2) PCT).
- 2.1 Claims 1-14, 28-31 appear to be novel over the cited prior art. Document D1 shows that ectopic expression of a dominant negative mutant of Dp110 (DP110<sup>D954A</sup>) reduced cell size in the wings (Fig. 3) and eyes (Fig. 4) resulting in smaller wings and eyes. Since the claims are restricted to *chico* mutants, D1 does not affect novelty.

2.2 Claims 15-27 lack novelty over D2. As revealed in the description p. 3-4, chico¹ is a synonym for the P element induced mutation fs(2)4¹ disclosed in D2. The description states that "two further phenotypes associated with the defect fs(2)4¹ could be observed: Homozygous animals are reduced in size and adult flies have increased lipid levels". This statement unambiguously reveals that the genotypes of fs(2)4¹ and chico are the same. Accordingly, it appears that so far undiscovered (or never reported) phenotypic traits of fs(2)4¹ were found.

For assessment of novelty of the product claims, said phenotypic traits are of no relevance. Said traits represent non-distinctive characteristics which do not imply a particular form of the product. Since the known and claimed products are identical in all respects, an objection of novelty arises (cf PCT Guidelines Section IV: III-4.8 and IV-7.6).

The same applies with regards to the sequence data included in claims 6, 7.

As a consequence of the above, D2 is prejudicial to novelty of the product claims 15-27.

## 3. Inventive step (Art. 33(3) PCT).

Claims 1-14, 28-31 are considered to involve an inventive step within the meaning or Art. 33 (3) PCT.

Said claims concern screening methods using chico mutants.

The meeting abstract D3 describes the phenotype of *chico* mutants and reveals the function of the gene product as insulin receptor substrate. However, D3 does neither provide any information regarding the gene locus of *chico* nor does it make a link between fs(2)4¹ and *chico*. The information provided in D3 is therefore insufficient for the skilled person to generate *chico* mutants for use in the screening methods of said claims.

Thus, D3 is not an enabling disclosure and is therefore not considered relevant for evaluation of inventive step of claims.

Starting from D2, the skilled person would not have derived the phenotype of the reduced body size and therefore would not have considered the use of the mutant for the screening methods recited in claims 1-14, 28-31.

## Re Item VIII

Certain observations on the international application

- 1. Claims 15-27 are unclear because the subject-matter for which protection is sought is not precisely defined. In the present draft, claim 15 refers to an "insect mutant having at most one wild type chico gene". This can be understood as extending to insects having no chico gene at all, i.e. insects which naturally do not have the chico gene and have some mutation in another gene. Thus, claim 15 and appending claims 16-27 cover a large group of insect mutants, for which there is no support (Art. 6 PCT) and which is not unambiguously distinguishable from the prior art (Art. 6 and Art. 33 (2) PCT).
- 2. Claims 1, 2, 4, 5, 12-24, 26-31 are not supported by the description as required by Art. 6 PCT. Said claims refer to mutants of any insect, whereas the examples in the description concern Drosophila mutants only. The contribution of the present application clearly belongs to the field of Drosophila mutants and does not warrant broadening of the whole concept to all insects.
- Claims 1-5, 8, 10-18, 21-31 refer to a chico mutant. The mutant drosophila or insect is specified solely by a name which, however, is meaningless to the person skilled in the art. Although the mutation has been described in the prior art, it has been given other names therein. It is therefore not clear what the subject matter is and the claims are not enabled (Art. 5/6 PCT).
  - The PCT Guidelines state in Section IV, II-4.16: "The use of proper names or similar words to refer to materials or articles is undesirable insofar as such words merely denote origin or where they relate to a range of different products. If such a word is used, then in order to satisfy the requirements of Article 5, the product must normally be sufficiently identified without reliance upon the word, to enable the invention to be carried out by a person skilled in the art. However, where such words have become internationally accepted as standard descriptive terms and have acquired a precise meaning (for example "Bowden" cable, "Bellville" washer), they may be allowed without further identification of the product to which they relate."

## Claims

1. A method for searching for compounds or mutations interacting directly or indirectly with the 5 insulin signaling pathway, characterized in that a viable insect is treated with at least one compound or with at least one mutation generating means, and that the effect of such treatment on the body size and/or cell size and/or development time and/or lipid level is determined 10 whereby alterations of the body size and/or cell size and/or development time and/or lipid level are detectable in at least part of the animal.

2. The method of claim 1 characterized in that the viable insect is a viable chico mutant insect. 15 whereby said mutant comprises at most one wild-type chico gene.

3. The method of claim 2 wherein the mutant is a Drosophila mutant and wherein said mutant is treated in the egg or larvae stadium with said compound or 20 compound generating means.

4. The method of claim 2 or 3 wherein the mutant does not comprise a wild-type chico gene.

5. The method of claim 2 or 3 wherein the Drosophila mutant comprises one wild-type chico gene.

6. The method of claim 5 wherein the wild-25 type chico gene encodes the amino acid sequence of Table 1 (SEQ. ID. NO. 2, 3).

7. The method of claim 6, wherein the wildtype chico gene is the genomic or the cDNA sequence 30 represented in Table 1 (SEQ. ID. NO. 1, 2) or Table 2 (SEO. ID. NO. 4).

8. The method of anyone of claims 2 to 7 wherein the Drosophila mutant comprises at least one chico mutation with lacking or reduced activity compared 35 to wild-type chico.

9. The method of claim 7 wherein the chico mutation is the mutation described in Figure 3A.

- 10. The method of anyone of claims 2 to 9 wherein the Drosophila lacks at least one chico gene.
- 11. The method of claim 10 wherein the mutant lacks both *chico* genes.
- 12. The method of anyone of claims 1 to 11 wherein the compound is a compound for the treatment of diabetes type 2.
- 13. The method of anyone of claims 1 to 12, wherein the alteration of the body size and/or the cell
- wherein the alteration of the body size and/or the terr

  10 size and/or the development time and/or the lipid level
  is detectable in the whole animal.
- 14. The method of anyone of claims 1 to 12, wherein the alteration of the body size and/or the cell size and/or the development time and/or the lipid level is detectable in the head region only.
  - 15. A viable insect mutant comprising at most one wild-type chico gene in at least a part of its body. 16. The mutant of claim 15 that does not
  - comprise as sole *chico* genes two *chico*<sup>1</sup> genes.
- 20 17. The mutant of claim 15 or 16 that does not comprise a wild-type chico gene.
  - 18. The mutant of claim 15 or 16 that comprises one wild-type chico gene.
- 19. The mutant of claim 18 wherein the wild-25 type chico gene encodes the amino acid sequence of Table 1 (SEQ. ID. NO. 2, 3).
- 20. The mutant of claim 19, wherein the wildtype chico gene is the genomic or the cDNA sequence represented in Table 2 (SEQ. ID. NO. 4) or Table 1 (SEQ. 30 ID. NO. 1, 2).
  - 21. The mutant of anyone of claims 15 to 20 comprising at least one *chico* mutation with lacking or reduced activity compared to wild-type *chico*.
- 22. The mutant of claim 21 wherein the *chico* 35 mutation is the mutation described in Figure 3A.
  - 23. The mutant of anyone of claims 15 to 22 lacking at least one *chico* gene.

24. The mutant of claim 15 lacking both chico

genes.  ${\it 25. \ The \ mutant \ of \ anyone \ of \ claims \ 15 \ to \ 24}$  which is a fly mutant, in particular a Drosophila mutant.

26. The mutant of anyone of claims 15 to 25, wherein at most one wild-type *chico* gene is found in the

whole body of the insect.

27. The mutant of anyone of claims 15 to 25,

wherein at most one wild-type chico gene is found in the 10 head region of the insect only.

28. Use of an insect according to anyone of claims 15 to 27 as a means in screening compounds for modulating diseases.

29. Use of an insect according to anyone of 15 claims 15 to 27 as a means for searching for mutations involved directly or indirectly in the insulin signaling pathway.

30. Use according to claim 22 or 23, characterized in that the disease is diabetes type 2.

20 31. A method for generating a mutant insect, characterized in that adult animals, in particular males, are treated with a mutation generating means under mutation generating conditions, that thus treated insects are crossed to wild-type or mutant insects, in particular 25 chico mutant insects, and that viable offsprings with altered cell number and /or cell size and/or developmental time and/or lipid levels are cultivated under suitable conditions.

## (19) World Intellectual Property Organization International Bureau



(43) International Publication Date 28 December 2000 (28.12.2000)

PCT

# (10) International Publication Number WO 00/78940 A1

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- (21) International Application Number: PCT/IB99/01166
- (22) International Filing Date: 22 June 1999 (22.06.1999)
- (25) Filing Language:

English

- (26) Publication Language:
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- (71) Applicant (for all designated States except US): UNI-VERSITÄT ZÜRICH [CH/CH]; Winterthurerstrasse 190, CH-8057 Zürich (CH).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): HAFEN, Ernst [CH/CH]; Zoologisches Institut, Winterthurerstrasse 190, CH-8057 Zürich (CH).
- (74) Agent: E. BLUM & CO.; Vorderberg 11, CH-8044 Zürich (CH).

- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, AW, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TI, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH. GM. KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

### Published:

With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

78940 A1

PCT/IB 99/01166

Relevant to claim No.

1

A. CLASSIFICATION OF SUBJECT	C07K14/435	A01K67/033

According to International Patent Classification (IPC) or to both national classification and IPC

Category \* Citation of document, with indication, where appropriate, of the relevant passages

LEEVERS, S. ET AL.: "The Drosophila

phosphoinositide 3-kinase Dp110 promotes

## B. FIELDS SEARCHED

Υ

Minimum documentation searched (classification system followed by classification symbols) IPC 7 A01K C07K

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

	phosphoinositide 3-kinase Dpl10 cell growth." EMBO JOURNAL, vol. 15, no. 23, 2 December 1996 (1996-12-02), pa 6584-6594, XPO00877417 EYNSHAM, OXFORD GB the whole document				
Υ	US 4 774 321 A (ROSNER MARSHA R 27 September 1988 (1988-09-27) the whole document	ET AL)	1		
		-/			
	ther documents are listed in the continuation of box C.	Patent family members are listed			
"A" docum	nent defining the general state of the art which is not dered to be of particular relevance	or priority date and not in conflict with the appacation but cated to understand the principle or theory underlying the invention			
"E" eartier	document but published on or after the international date	"X" document of particular relevance; the	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone		
which	nent which may throw doubts on priority claim(s) or his cited to establish the publication date of another on or other special reason (as specified) ment referring to an oral disclosure, use, exhibition or	"Y" document of particular relevance; the cannot be considered to involve an	claimed invention nventive step when the note other such docu-		
*P* docur	ment referring to an oral disclosure, due, which was a referring to an oral disclosure, due to the international sting date but than the priority date claimed	ments, such combination being obvious to a person skilled in the art.  "&" document member of the same patent family			
	e actual completion of the international search	Date of mailing of the international s	Date of mailing of the international search report		
	10 March 2000	28/03/2000			
Name and	d mailing address of the ISA	Authorized officer			
	European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tol. (+31-70) 340-2040, Tx 31 651 epo ni, Fax: (+31-70) 340-3016	Chambonnet, F			
	AZZTO (second sheet) (July 1992)				

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PCT/TR 99/01166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages 1 THE I, HANNIGAN GE, COWLEY GS, REGINALD S, ZHONG Y, GUSELLA JF, HARIHARAN IK, Α BERNARDS A. : "Rescue of a Drosophila NF1 mutant phenotype by protein kinase A." SCIENCE. vol. 276, no. 5313, 2 May 1997 (1997-05-02), pages 791-794, XP000877265 the whole document WO 99 05258 A (ARCH DEV CORP ;UNIV Υ CALIFORNIA (US)) 4 February 1999 (1999-02-04) claims 22-24 LEROITH D: "A novel Drosophila insulin receptor: fly in the ointment or evolutionary conservation?" ENDOCRINOLOGY. 1995 JUN; 136(6): 2355-6. . vol. 136, no. 6, June 1995 (1995-06), pages 2355-2356, XP000884907 the whole document 1 - 31BOHNI R, RIESGO-ESCOVAR J, OLDHAM S, BROGIOLO W, STOCKER H, ANDRUSS BF, BECKINGHAM K, HAFEN E. : "Autonomous control of cell and organ size by CHICO, a Drosophila homolog of vertebrate IRS1-4." vol. 97, no. 7, 25 June 1999 (1999-06-25), pages 865-875, XP000877263 the whole document EDGAR BA. : "From small flies come big Т discoveries about size control." NAT CELL BIOL. 1999 DEC;1(8):E191-E193., XP000889763 the whole document LEEVERS SJ.: "Perspectives: cell biology. Т All creatures great and small.' SCIENCE. vol. 285, no. 5436, 24 September 1999 (1999-09-24), pages 2082-2083, XP000877264 the whole document WEINKOVE D, LEEVERS SJ. : "The genetic Т control of organ growth: insights from Drosophila." CURR OPIN GENET DEV. . vol. 10, no. 1, February 2000 (2000-02), pages 75-80, XP000889771 the whole document -/--

1



Inter: Application

PCT/IB 99/01166 C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Category Citation of document, with indication where appropriate, of the relevant passages MOLZ L ET AL: "CPK IS A NOVEL CLASS OF DROSOPHILA PTDINS 3-KINASE CONTAINING A C2 DOMAIN" JOURNAL OF BIOLOGICAL CHEMISTRY, US, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 271, no. 23, 7 June 1996 (1996-06-07), pages 13892-13899, XP002073709 ISSN: 0021-9258

International application No.

INTERNATIONAL SEARCH REPORT PCT/IB 99/01166

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet) This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: 1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 1 to 14 are directed to a method of treatment of the animal body, the search has been carried out and based on the alleged effects of the animal. CHARTIS INVO.

because they relate to parts of the international Application that do not comply with the prescribed requirements to such 2. Claims Nos.: an extent that no meaningful International Search can be carried out, specifically: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). Box il Observations where unity of invention is lacking (Continuation of item 2 of first sheet) This International Searching Authority found multiple inventions in this international application, as follows: As all required additional search fees were timely paid by the applicant, this international Search Report covers all searchable claims. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee. As only some of the required additional search fees were timely paid by the applicant, this international Search Report 3. covers only those claims for which fees were paid, specifically claims Nos.: No required additional search fees were timely paid by the applicant. Consequently, this international Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: The additional search tees were accompanied by the applicant's protest. Remark on Protest No protest accompanied the payment of additional search tees.

# INTERNAT AL SEARCH REPORT Inter Application No.

tre	ormation on patent family memb	ers		PCT/IB	99/01166
Patent document cited in search report	Publication date	Pa	atent family nember(s)	,	Publication date
US 4774321 A	27-09-1988	NONE			
WO 9905258 A	04-02-1999	AU	84082	298 A	16-02-1999

10/019,098

PATENT COOPERATION TREATY

REC'D 27 FEB 2002

WIPO PCT

# **PCT** INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION  See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)				
02559PC					
International application No.	International filing date (day/month	(22/06/19997			
PCT/IB99/01166	22/06/1999	<u> </u>			
International Patent Classification (IPC) or na C12N15/00	tional classification and IPC				
Applicant					
UNIVERSITÄT ZÜRICH et al.					
This international preliminary exam and is transmitted to the applicant a	ination report has been prepared according to Article 36.	by this International Preliminary Examining Authority			
2. This REPORT consists of a total of	6 sheets, including this cover s	heet.			
	ed by ANNEXES, i.e. sheets of the sis for this report and/or sheets of 07 of the Administrative Instruct	ne description, claims and/or drawings which have containing rectifications made before this Authority ons under the PCT).			
These annexes consist of a total o	f 3 sheets.				
This report contains indications rel	lating to the following items:				
∣ ⊠ Basis of the report					
Priority		welly, inventive step and industrial applicability			
		velty, inventive step and industrial applicability			
IV  Lack of unity of invent	tion	and the inventive step or industrial applicability:			
V ☐ Reasoned statement citations and explana	under Article 35(2) with regard to tions suporting such statement	novelty, inventive step or industrial applicability;			
VI ☐ Certain documents c					
VII Certain defects in the					
	on the international application				
Date of submission of the demand	Date o	of completion of this report			
08/01/2001					
Name and mailing address of the internation preliminary examining authority:	onal Autho	rized officer			
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 5238		rein, M			
Fax +49 89 2399 - 4465	Telep	hone No +49 89 2399 7358			

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB99/01166

۱.	Basis	of the	report
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the and	rec l ar	egard to the elenceiving Office in e not annexed to iption, pages:	nents of the international a response to an invitation u o this report since they do	application (Replace inder Article 14 are not contain amendr	ement sheets whic referred to in this nents (Rules 70.1	th have been furnished to report as "originally filed" 6 and 70.17)):
1-4	4		as originally filed			
		s, No.:		30/08/2001	with letter of	29/08/2001
1-3	11		as received on	00/00/2007		
Dr	awi	ings, sheets:				
1/8	8-8/	78	as originally filed			
Sa		ence listing par	rt of the description, pag	es:		
1-	16,	as originally file	ď			
la	ngu nes	age in which the e elements were	e international application as	this Authority in the	following languag	e: , which is:
	1 1	the language of	a translation furnished for	the purposes of the	international sear	ch (under Rule 23.1(b)).
	٠.	the lenguage of	publication of the internation	onal application (un	der Rule 48.3(b)).	
		the language of 55.2 and/or 55.3	a translation furnished for	the purposes of inte	ernational prelimin	ary examination (under Rule
3. <b>V</b> ir	√ith nter	regard to any <b>n</b> national prelimir	nucleotide and/or amino a nary examination was carri	ed out on the basis	losed in the intern of the sequence I	ational application, the isting:
D	3	contained in the	international application is	n written form.		
0	3	filed together wi	ith the international applica	ation in computer rea	adable form.	
[	_	furnished subse	equently to this Authority in	written form.		
	3	funciohed subse	aquently to this Authority in	computer readable	form.	
	3	The statement	that the subsequently furn	ished written sequer een furnished.	nce listing does no	ot go beyond the disclosure in
I		The statement listing has been	that the information record	led in computer read	dable form is iden	ical to the written sequence
4.	The	amendments h	ave resulted in the cancell	ation of:		

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB99/01166

	the description,	pages:			
	the claims,	Nos.:			
	the drawings,	sheets:			
5.	This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):				
	(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)				

- 6. Additional observations, if necessary:
- V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- 1. Statement

 Novelty (N)
 Yes: Claims No: Claims
 1-14, 28-31 15-27

 Inventive step (IS)
 Yes: Claims No: Claims 1-14, 28-31 15-27

Industrial applicability (IA) Yes: Claims 1-31 No: Claims

Citations and explanations see separate sheet

# VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

Reference is made to the following documents:

- D1: Leevers, S. et al.: 'The Drosophila phosphoinositide 3-kinase Dp110 promotes cell growth,' EMBO JOURNAL, vol. 15, no. 23, 2 December 1996 (1996-12-02), pages 6584-6594. XP000877417 EYNSHAM, OXFORD GB
- D2: Berg C A; Spradling A C: Studies on the rate and site-specificity of p element transposition. GENETICS 127, 3, 515-524 (1991), cited in the application
- D3: Riesgo-Escovar J. R. et al.: chico, a Drosophila homologue of mammalian insulin receptor substrate (IRS) genes, is required cell-autonomously for cell size. 39th Annual Drosophila Research Conference, 1998: 32, p. a12.

## Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- The present application relates to Drosophila mutants with reduced body or cell size. 1. Mutations or null alleles of chico result in reduced body size. The chico gene product is a homologue of mammalian insulin receptor substrate (IRS) proteins. Mutant flies are thus useful in screening for compounds interacting with the insulin signalling pathway.
- Novelty (Art. 33 (2) PCT). 2.
- 2.1 Claims 1-14, 28-31 appear to be novel over the cited prior art. Document D1 shows that ectopic expression of a dominant negative mutant of Dp110 (DP110<sup>D954A</sup>) reduced cell size in the wings (Fig. 3) and eyes (Fig. 4) resulting in smaller wings and eyes. Since the claims are restricted to chico mutants, D1 does not affect novelty.

# 2.2 Claims 15-27 lack novelty over D2. As revealed in the description p. 3-4, chico¹ is a synonym for the P element induced mutation fs(2)4¹ disclosed in D2. The description states that "two further phenotypes associated with the defect fs(2)4¹ could be observed: Homozygous animals are reduced in size and adult flies have increased lipid levels". This statement unambiguously reveals that the genotypes of fs(2)4¹ and chico are the same. Accordingly, it appears that so far undiscovered (or never reported) phenotypic traits of fs(2)4¹ were found.

For assessment of novelty of the product claims, said phenotypic traits are of no relevance. Said traits represent non-distinctive characteristics which do not imply a particular form of the product. Since the known and claimed products are identical in all respects, an objection of novelty arises (cf PCT Guidelines Section IV: III-4.8 and IV-7.6).

The same applies with regards to the sequence data included in claims 6, 7.

As a consequence of the above, D2 is prejudicial to novelty of the product claims 15-27.

# 3. Inventive step (Art. 33(3) PCT).

Claims 1-14, 28-31 are considered to involve an inventive step within the meaning or Art. 33 (3) PCT.

Said claims concern screening methods using chico mutants.

The meeting abstract D3 describes the phenotype of *chico* mutants and reveals the function of the gene product as insulin receptor substrate. However, D3 does neither provide any information regarding the gene locus of *chico* nor does it make a link between fs(2)4¹ and *chico*. The information provided in D3 is therefore insufficient for the skilled person to generate *chico* mutants for use in the screening methods of said claims.

Thus, D3 is not an enabling disclosure and is therefore not considered relevant for evaluation of inventive step of claims.

Starting from D2, the skilled person would not have derived the phenotype of the reduced body size and therefore would not have considered the use of the mutant for the screening methods recited in claims 1-14, 28-31.

# **EXAMINATION REPORT - SEPARATE SHEET**

## Re Item VIII

Certain observations on the international application

- Claims 15-27 are unclear because the subject-matter for which protection is sought 1. is not precisely defined.
  - In the present draft, claim 15 refers to an "insect mutant having at most one wild type chico gene". This can be understood as extending to insects having no chico gene at all, i.e. insects which naturally do not have the chico gene and have some mutation in another gene. Thus, claim 15 and appending claims 16-27 cover a large group of insect mutants, for which there is no support (Art. 6 PCT) and which is not unambiguously distinguishable from the prior art (Art. 6 and Art. 33 (2) PCT).
- Claims 1, 2, 4, 5, 12-24, 26-31 are not supported by the description as required by 2. Art. 6 PCT. Said claims refer to mutants of any insect, whereas the examples in the description concern Drosophila mutants only. The contribution of the present application clearly belongs to the field of Drosophila mutants and does not warrant broadening of the whole concept to all insects.
- Claims 1-5, 8, 10-18, 21-31 refer to a chico mutant. The mutant drosophila or insect 3. is specified solely by a name which, however, is meaningless to the person skilled in the art. Although the mutation has been described in the prior art, it has been given other names therein. It is therefore not clear what the subject matter is and the claims are not enabled (Art. 5/6 PCT).
  - The PCT Guidelines state in Section IV, II-4.16: "The use of proper names or similar words to refer to materials or articles is undesirable insofar as such words merely denote origin or where they relate to a range of different products. If such a word is used, then in order to satisfy the requirements of Article 5, the product must normally be sufficiently identified without reliance upon the word, to enable the invention to be carried out by a person skilled in the art. However, where such words have become internationally accepted as standard descriptive terms and have acquired a precise meaning (for example "Bowden" cable, "Bellville" washer), they may be allowed without further identification of the product to which they relate.".

## Claims

- 1. A method for searching for compounds or mutations interacting directly or indirectly with the insulin signaling pathway, characterized in that a viable chico mutant insect is treated with at least one compound or with at least one mutation generating means, and that the effect of such treatment on the body size and/or cell size and/or development time and/or lipid level is determined whereby alterations of the body size and/or cell size and/or development time and/or lipid level are detectable in at least part of the animal.
- 2. The method of claim 1 characterized in that the viable chico mutant insect comprises at most one wild-type chico gene.
  - 3. The method of claim 2 wherein the mutant is a Drosophila mutant and wherein said mutant is treated in the egg or larvae stadium with said compound or compound generating means.
- 20 4. The method of claim 2 or 3 wherein the mutant does not comprise a wild-type chico gene.
  - 5. The method of claim 2 or 3 wherein the Drosophila mutant comprises one wild-type chico gene.
- 6. The method of claim 5 wherein the wild-25 type chico gene encodes the amino acid sequence of Table
  - 1 (SEQ. ID. NO. 2, 3).
    7. The method of claim 6, wherein the wild-
- 7. The method of claim 6, wherein the wilds type chico gene is the genomic or the cDNA sequence represented in Table 1 (SEQ. ID. NO. 1, 2) or Table 2
  30 (SEQ. ID. NO. 4).
  - 8. The method of anyone of claims 2 to 7 wherein the Drosophila mutant comprises at least one chico mutation with lacking or reduced activity compared to wild-type chico.
  - The method of claim 7 wherein the chico mutation is the mutation described in Figure 3A.

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- 10. The method of anyone of claims 2 to 9 wherein the Drosophila lacks at least one chico gene.
- 11. The method of claim 10 wherein the mutant lacks both chico genes.
- 5 12. The method of anyone of claims 1 to 11 wherein the compound is a compound for the treatment of diabetes type 2.
- 13. The method of anyone of claims 1 to 12, wherein the alteration of the body size and/or the cell size and/or the development time and/or the lipid level is detectable in the whole animal.
- 14. The method of anyone of claims 1 to 12, wherein the alteration of the body size and/or the cell size and/or the development time and/or the lipid level is detectable in the head region only.
  - 15. A viable insect mutant comprising at most one wild-type *chico* gene in at least a part of its body and said at least one part of the body shows reduced size.
- 16. The mutant of claim 15 that does not comprise as sole *chico* genes two *chico*; genes.

  17. The mutant of claim 15 or 16 that does not comprise a wild-type *chico* gene.
  - 18. The mutant of claim 15 or 16 that
- 25 comprises one wild-type chico gene. 19. The mutant of claim 18 wherein the wildtype chico gene encodes the amino acid sequence of Table
  - 1 (SEQ. ID. NO. 2, 3).

    20. The mutant of claim 19, wherein the wild-
- 30 type chico gene is the genomic or the cDNA sequence represented in Table 2 (SEQ. ID. NO. 4) or Table 1 (SEQ. ID. NO. 1, 2).
- 21. The mutant of anyone of claims 15 to 20 comprising at least one chico mutation with lacking or reduced activity compared to wild-type chico.
  - 22. The mutant of claim 21 wherein the  ${\it chico}$  mutation is the mutation described in Figure 3A.

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23. The mutant of anyone of claims 15 to 22 lacking at least one chico gene.

24. The mutant of claim 15 lacking both *chico* genes.

25. The mutant of anyone of claims 15 to 24 which is a fly mutant, in particular a Drosophila mutant.

26. The mutant of anyone of claims 15 to 25, wherein at most one wild-type chico gene is found in the whole body of the insect.

27. The mutant of anyone of claims 15 to 25, wherein at most one wild-type *chico* gene is found in the head region of the insect only.

28. Use of an insect according to anyone of claims 15 to 27 as a means in screening compounds for modulating diseases.

29. Use of an insect according to anyone of claims 15 to 27 as a means for searching for mutations involved directly or indirectly in the insulin signaling pathway.

20 30. Use according to claim 22 or 23, characterized in that the disease is diabetes type 2.

31. A method for generating a mutant insect, characterized in that adult animals, in particular males, are treated with a mutation generating means under mutation generating conditions, that thus treated insects are crossed to wild-type or mutant insects, in particular chico mutant insects, and that viable offsprings with altered cell number and /or cell size and/or developmental time and/or lipid levels are cultivated

30 under suitable conditions.



(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of (Form PCT/ISA/22	Transmittal of Internation (20) as well as, where app	onal Search Report plicable, Item 5 below.		
02559PC International application No.	International filing date (da	y/month/year) I	(Earliest) Priority Date	(day/month/year)		
PCT/IB 99/01166	22/06/19	99				
Applicant						
UNIVERSITÄT ZÜRICH et al.						
This international Search Report has been according to Article 18. A copy is being tra	n prepared by this internation insmitted to the international	nal Searching Auth Bureau.	ority and is transmitted t	to the applicant		
This International Search Report consists	of a total of 6	sheets.				
It is also accompanied by	a copy of each prior art doc		report.			
Basis of the report		and and the state of	the and the desired the second	unilication in the		
<ul> <li>With regard to the language, the language in which it was filed, uni</li> </ul>	less otherwise indicated und	er this item.				
Authority (Rule 23.1(b)).	vas carried out on the basis of					
b. With regard to any nucleotide an	d/or amino acid sequence	disclosed in the in	nternational application, t	the international search		
was carried out on the basis of the	e sequence listing : onal application in written for	m.				
	emational application in com		n.			
	this Authority in written for					
	this Authority in computer r					
the statement that the su	bsequently furnished written as filed has been furnished.		loes not go beyond the d	fisciosure in the		
	formation recorded in compu	ter readable form k	s identical to the written	sequence listing has been		
2. X Certain claims were fou	und unsearchable (See Box	1).				
3. Unity of invention is lec						
4. With regard to the title,						
	ubmitted by the applicant.					
The text has been established						
IN VIVO INSECT MODEL SYSTEM FOR TYPE-2 DIABETES						
5. With regard to the abstract,						
the text is approved as submitted by the applicant.						
the total been been contabil	ished, according to Rule 38.5 ne date of mailing of this inte	2(b), by this Author mational search re	ity as it appears in Box i port, submit comments t	III. The applicant may, to this Authority.		
6. The figure of the drawings to be put						
as suggested by the app				None of the figures.		
because the applicant fa	illed to suggest a figure.					
because this figure bette	er characterizes the invention	٦.				



onal application No.

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet) This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: 1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 1 to 14 are directed to a method of treatment of the animal body, the search has been carried out and based on the alleged effects of the animal. 2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international Search can be carried out, specifically: 3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet) This international Searching Authority found multiple inventions in this international application, as follows: As all required additional search fees were timely paid by the applicant, this international Search Report covers all 1. searchable claims. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment 2. of any additional fee. As only some of the required additional search fees were timely paid by the applicant, this international Search Report covers only those claims for which fees were paid, specifically claims Nos.: 3. [ No required additional search fees were timely paid by the applicant. Consequently, this international Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: The additional search fees were accompanied by the applicant's protest. Remark on Protest No protest accompanied the payment of additional search fees.

onal application No.
PCT/IB 99/01166

Box III TEXT OF THE ABSTRACT (Continuation of Item 5 of the first sheet)

An in vivo monitory system for e.g. investigating defects in the insulin signaling pathway and screening for drugs suitable for the treatment of such defects, in particular a system using Drosophila chico mutants, is disclosed as well as a method for using such a system and for its generation.

Application No **3** 99/01166

Relevant to claim No.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/00 C07K14/435 A01K67/033

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Minimum documentation searched (classification system followed by classification symbols)  $IPC \ 7 \ A01K \ C07K$ 

Category Citation of document, with indication, where appropriate, of the relevant passages LEEVERS, S. ET AL.: "The Drosophila

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

T	phosphoinositide 3-kinase Dp110 cell growth." EMBO JOURNAL, vol. 15, no. 23, 2 December 1996 (1996-12-02), pa 6584-6594, YD000877417 EYNSHAM, OXFORD GB the whole document			
Y	US 4 774 321 A (ROSNER MARSHA R 27 September 1988 (1988-09-27) the whole document	ET AL)	1	
		-/		
*A* documer conside	er documents are listed in the continuation of box C.  egories of cited documents:  Int defining the general state of the art which is not seed to be of particular reference.	T later document published after the in or priority date and not in conflict will ched to understand the principle or invention.	ternational filing date th the application but theory underlying the	
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later th	an the priority date claimed	"&" document member of the same pate  Date of mailing of the international a		
	0 March 2000	28/03/2000		
Name and m	naling address of the ISA European Patent Office, P.B. 5818 Patentiaan 2 NI. — 2260 HV Rijswift Tet. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Chambonnet, F		
orm PCT/ISA/2	210 (second sheet) (July 1992)	page 1 o		

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PC 99/01166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages THE I, HANNIGAN GE, COWLEY GS, REGINALD S, 1 Α ZHONG Y, GUSELLA JF, HARIHARAN IK. BERNARDS A. : "Rescue of a Drosophila NF1 mutant phenotype by protein kinase A. SCIENCE. , vol. 276, no. 5313, 2 May 1997 (1997-05-02), pages 791-794. XP000877265 the whole document 1 WO 99 05258 A (ARCH DEV CORP ;UNIV Υ CALIFORNIA (US)) 4 February 1999 (1999-02-04) claims 22-24 1 IFROITH D: "A novel Drosophila insulin Α receptor: fly in the ointment or evolutionary conservation?" ENDOCRINOLOGY. 1995 JUN; 136(6):2355-6., vol. 136, no. 6, June 1995 (1995-06), pages 2355-2356, XP000884907 the whole document BOHNI R, RIESGO-ESCOVAR J, OLDHAM S, 1 - 31T BROGIOLO W, STOCKER H, ANDRUSS BF, BECKINGHAM K, HAFEN E. : "Autonomous control of cell and organ size by CHICO, a Drosophila homolog of vertebrate IRS1-4. CELL. vol. 97, no. 7, 25 June 1999 (1999-06-25), pages 865-875, XP000877263 the whole document 1 Т FDGAR BA. : "From small flies come big discoveries about size control.' NAT CELL BIOL. 1999 DEC;1(8):E191-E193., XP000889763 the whole document 1 LEEVERS SJ.: "Perspectives: cell biology. T All creatures great and small." SCIENCE. vol. 285, no. 5436. 24 September 1999 (1999-09-24), pages 2082-2083, XP000877264 the whole document WEINKOVE D, LEEVERS SJ. : "The genetic 1 Т control of organ growth: insights from Drosophila." CURR OPIN GENET DEV. , vol. 10, no. 1, February 2000 (2000-02), pages 75-80, XP000889771 the whole document -/--

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PC 99/01166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT Category Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. MOLZ L ET AL: "CPK IS A NOVEL CLASS OF Α DROSOPHILA PTDINS 3-KINASE CONTAINING A C2 DOMAIN" JOURNAL OF BIOLOGICAL CHEMISTRY, US, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, vol. 271, no. 23, 7 June 1996 (1996-06-07), pages 13892-13899, XP002073709 ISSN: 0021-9258

nformann patent family members

Internal Application No PC1 28 99/01166

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Ī	US 4774321	Α	27-09-1988	NONE	
İ	WO 9905258	A	04-02-1999	AU 8408298 A	16-02-1999